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The impact of Computed Tomography Enterography and Magnetic Resonance Enterography on the outcome of patients with Crohn's Disease / O impacto da Enterografia por Tomografia Computorizada e por Ressonância Magnética no outcome dos doentes com Doença de Crohn

março, 2017

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The impact of Computed Tomography Enterography and Magnetic Resonance Enterography on the outcome of patients with Crohn's Disease

ORIENTADOR

Professor Doutor Fernando Magro

COORIENTADOR (se aplicável)

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Faculdade de Medicina da Universidade do Porto, 19/03/2017

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The impact of Computed Tomography Enterography and Magnetic Resonance Enterography on the outcome of patients with Crohn's Disease

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Abstract

Background: In the last few decades, Computed Tomography Enterography **(**CTE) and Magnetic Resonance Enterography (MRE) have become crucial weapons for the evaluation of patients with Crohn's Disease (CD). Despite the many studies on the role of cross sectional imaging in the diagnosis and assessment of CD activity, there are few related to their impact on the patients' outcome.

Methods: The study group for this retrospective study was composed of 349 patients previously diagnosed with CD, who underwent CTE/MRE from January 2010 to December 2015. Epidemiological and clinical data were collected from patients' clinical reports as well as CTE and MRE findings and their influence on management plan. Chi-square test and Fisher's exact test were used to evaluate the statistical significance.

Results: 349 cases were evaluated, of which 85% underwent CTE and 15% MRE. Overall, 60 patients had no CTE/MRE evidence of active disease and 289 had abnormal exams, of which the most frequent findings included bowel wall thickening and mural hyperenhancement. The CTE and MRE studies influenced a change in management in 40% of patients, leading more frequently to the introduction of immunomodulators (10%), anti-TNFα agents (8%) and corticosteroids (6%). Mural stratification was the only sign shown to be strongly related to change in management.

Conclusions: CTE and MRE played a decisive role in the outcome, leading to a therapeutic change in 40% of patients, and mural stratification, a sign of gravity, was strongly related with the outcome, leading to change in management in 46% of patients. Our findings further support the use of this imaging techniques in CD management algorithms.

Key Words: "Crohn's Disease", "Magnetic Resonance", "Computed Tomographic", "Enterography" and "Management Plan".

Introduction

Crohn's Disease (CD) is a chronic inflammatory bowel disease with a peak incidence between the second and fourth decades of life, characterized by an unpredictable course, marked by relapses and remissions.[1] It can affect any part of the gastrointestinal tract, from the mouth to the anus, with about 80% of cases involving the small bowel, particularly the terminal ileum.[2] The inflammation manifests itself by ulceration, which can range from superficial lesions to deep ulcers, with areas of inflammation interspersed with regions of normal mucosa (skip lesions). The transmural nature of CD always leads to stricturing or penetrating disease with intestinal obstruction and formation of fistuleas and abscesses.[3] The annual incidence of Crohn's Disease is estimated at 12.7 per 100,000 people in Europe and 20.2 per 100,000 people in North America. Its increasing incidence in both developed and developing countries shows the emergency of CD as a global disease.[4]

Several clinical indices have been developed in order to assess and quantify the severity of the disease. The most commonly used are the CD Activity Index and the Harvey Bradshaw Index, which classify the disease from asymptomatic remission to severe disease.[5] With the recent introduction of effective medication, such as anti-TNF agents, "mucosal healing" is considered as the target of therapy for CD. This requires full disease assessment based not only on clinical and endoscopic data, but also on the findings of imaging techniques.[6]

Ileocolonoscopy is the gold standard for direct visualization of the colon's mucosa and for obtaining material for histological study through biopsies and it remains the ideal method for objective evaluation of disease activity in CD.[7,8] However, in addition to not being able to evaluate the trans-mural extent of the disease, another major limitation of endoscopy is the inability to classify the disease severity at the level of the small intestine or to evaluate extra-luminal complications.[5] Thus, cross-sectional imaging is becoming indispensable in the evaluation and classification of the severity of CD, since it allows the imaging of the entire gastrointestinal tract, observation of the bowel wall and evaluation of extra-intestinal complications, providing additional information and enabling clinicians to make more informed decisions regarding to patients' management plans.[9] In the last consensus of the European Crohn's and Colitis Organisation, Computed Tomography Enterography (CTE) and Magnetic Resonance

Enterography (MRE) are the imaging techniques recommended to determine the extent of CD in the small intestine.[10]

CTE is widely used in the diagnosis of CD and evaluation of disease activity. Nevertheless, this imaging technique resorts to ionizing radiation with an adverse cumulative effect for patients, which is of extreme importance in CD since it affects mainly young adults and has a course marked by frequent relapses. Therefore, a free-radiation alternative is preferred, as is the case of MRE.[7] There have been several studies comparing the effectiveness of MRE and CTE for detecting active inflammatory disease. A recent meta-analysis including 290 patients from 6 different studies diagnosed with CD showed that CTE and MRE have comparable sensitivity and specificity for demonstrating disease activity and detecting CD's complications.[11]

An accurate assessment of disease characteristics is essential for proper management of CD, with prognostic implications.[12] Treat-to-target strategies are viewed as essential to the goal of altering the natural history of CD.[13] With the increased use of cross sectional imaging in diagnosis and monitoring of CD, MRE-based severity scores have been developed and discussed. These severity scores can provide a better description of inflammatory lesions and severity assessment and may be useful in clinical practice to guide treatment decisions and in the evaluation of therapeutic efficacy. [13] Rimola et al[14] proposed and validated the most widely used severity score - "Magnetic Resonance Index of Activity" (MaRIA). This score takes into account bowel wall thickness, mucosal hyperenhancement and presence of edema and ulcers. [5] MaRIA score was shown to be highly correlated with the CD Endoscopic Index of Severity (CDEIS), the reference gold standard for endoscopic evidence of disease. [13]

Despite the many studies on the role of CTE and MRE in the diagnosis and detection of CD activity, there are few related to their impact on the outcome of these patients. [3] The objectives of the present study were to evaluate how CTE and MRE influence the clinician's therapeutic decision in patients with CD and to assess the impact of specific radiological signs in this decision.

Materials and Methods

This paper is based on a retrospective study of 349 patients of *Centro Hospitalar de São João* (CHSJ), with an established diagnosis of CD and who underwent CTE or MRE from January 2010 to December 2015. Patients with "suspected CD" as an indication were not included in this analysis. Patients with a diagnosis of Indeterminate Colitis or Ulcerative Colitis were excluded from our study. The cases in which more than 4 months had elapsed between the CTE or MRE evaluation and the change in management plans were also excluded.

The list of patients who underwent CTE or MRE between January 2010 and December 2015 was provided by the Radiology Department of CHSJ's. The clinical variables analyzed in our study were collected from the database of the G*rupo de Estudos de Doença Inflamatória Intestinal* (GEDII).

Of the 923 patients with inflammatory bowel disease who underwent CTE and ERM between 2010 and 2015 at our institution, 454 were excluded due to insufficient data for the analyses; 28 were excluded due to their diagnosis of Ulcerative Colitis or Undetermined Colitis; 19 were excluded because there was more than 4 months between the CTE or MRE assessment and the change in management, and 73 were excluded because these exams were performed with the purpose of aiding the diagnosis of CD.

Data Collection

Clinical and Demographic Data

Clinical data related to the Montreal Classification, which includes age at the diagnosis (A1 - ≤16 years old; A2 - 17-39 years old; and A3 - ≥40 years old); disease behavior (B1 – non stricturing non penetrating; B2 – stricturing; e B3 – penetrating; and p - perianal disease) and disease location (L1 - ileal; L2 - colonic; L3 - ileocolonic; and L4 – upper gastrointestinal tract), were collected. Clinically, this classification of CD has benefits in terms of patient counseling, assessment of disease prognosis, and providing support for the clinicians' decision of the most appropriate therapeutic plan for each disease subtype. [15,16]

Other data obtained included clinical data related to a family history of CD, clinical occurrences during the course of the disease ("Emergency Service", "Hospitalizations" and "Surgeries"), reasons and clinical circumstances of CTE or MRE evaluation ("Acute disease" or "Follow-up"; “Hospitalization” or "Ambulatory") and previous upper and/or low digestive endoscopy.

The baseline characteristics of the patients are represented in table 1.

Prior Endoscopic Study

In an attempt to avoid possible detection biases, previous endoscopic studies were evaluated, estimating their possible influence on patient outcome. We took into account the studies that were included in the consultation report, in which CTE or MRE were evaluated.

CTE and MRE Reports

Any signs pertaining to disease activity were collected based on the original CTE and MRE reports (multiple radiologists) by one of the authors, and And the doubts were discussed with the other authors. The CTE and MRE findings recorded included: “Bowel wall thickening”, “Mucosal enhancement”, “Mural stratification”, “Comb sign”, “Ulcer”, “Fistulae”, “Abscess” and “Stenosis” (table 2).

Follow-up and Patient Management

Pre- and post-CTE/MRE’s therapeutic plans collected from the clinical file of the patient, were analyzed for outcome evaluation. The drugs were grouped into eight categories: “Immunomodulators” (Azathioprine and Methotrexate), “Anti-TNFα agents” (Infliximab, Adalimumab and Golimumab); “Corticosteroids”; “Aminosalicylates”; “Polymeric diet”; and “Surgery”. Subsequently, possible outcomes were categorized as: "No change in management", "Escalating therapy" and "De-escalating therapy"; which were subcategorized as shown in table 3.

Statistical Analysis

Descriptive analysis included demographic and clinical data were reported as a number (percent) or median (minimum, maximum, percentiles) as appropriate. The Chi-square test and Fisher's exact test were used to calculate significant associations between the age of diagnosis, disease location and disease behavior and management; the cause and the context of CTE and MRE and management; endoscopy and management; CTE/MRE findings and management; and CTE/MRE findings and specific outcomes. *P* values less than 0.05 were considered significant.

Data were analyzed by using standard statistical software, SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Ethical Considerations

This study was approved by the The Ethical Commission for Health and authorized by the board of directors of *Centro Hospitalar de São João*.

Results

A total of 349 patients were included in the study [161 were females, 188 males, with a median age of 34 years old (ranging from 11 to 76; 25 percent were 24 and 75 percent were 47) and a median age at the time of diagnosis of 24 (25 percent were 24 and 75 percent were 47)] of which 85% underwent CTE and the remaining 15% MRE. Overall, 78% of CTE or MRE were performed with the objective of monitoring the disease activity, and the remaining 22% due to the manifestation of acute disease. In 83% of cases, CTE or MRE were performed as part of a consultation, while 17% were performed during hospitalization.

The majority of cases in the study (64%) received a diagnosis between the ages of 17 and 40, presenting a non-stricturing and non-penetrating behavior (30%) and a predominantly ileal (45%) and ileocolonic (44%) disease. Baseline characteristics of the patients included in our study are presented in table 1.

Prior Endoscopic Study

Of the 349 patients in the study, 122 (36%) had undergone at least one type of endoscopic exam. Of these 122 patients, 2 were subjected only to upper digestive endoscopy, 93 to lower digestive endoscopy, and 27 to both.

CTE and MRE Reports

Radiologists reported 57 different combinations of radiological signs with an average of 2.25 findings per CTE or MRE, ranging from 0 to 6 findings. The two most common findings included bowel wall thickening and mucosal enhancement (table 2).

Of the 349 CTE or MRE performed, 60 were considered normal, of which 70% maintained the treatment plan while 30% changed it. Of the 289 abnormal exams, 42% changed the management plan while 58% maintained the treatment plan. No statistically significant association was found between a normal or abnormal exam and outcome ($p = 0.087$).

Patient Management

After CTE or MRE, 139 patients (40%) changed the management plan, and some therapeutic decisions were included in more than one category. The three most frequent alterations included the introduction of an immunomodulator agent (10%), the introduction of an anti-TNFα agent (8%) and the introduction of a corticosteroid (6%). The results related to patients' outcome are expressed in table 4.

Association between clinical factors and endoscopic study with change in management

Age at the diagnosis, disease behavior and disease location were not statistically related to changes in management (A: p=0.121; B: p=0.696; p: p=0.090 L1-3: p=0.222; L4: p=0.812). On the contrary, reasons for CTE and MRE and context were significantly related to the outcome (*table* 5).

Regarding the endoscopy performed at the time of CTE and MRE, since no statistically significant association with the outcome (p = 0.089) was found, its correction was not necessary for the evaluation of the role of cross-sectional imaging in the patients' outcome.

Association between specific CTE or MRE findings and change in management

Tables 6 and 7 show the results regarding the association between specific radiological signs and possible outcomes. When comparing the specific CTE and MRE features with the outcomes (change in management plan and no change in management plan), of the 70 patients with normal CTE or MRE, 18 (30%) had a change in outcome; of which 20% the outcome consisted of escalating therapy and 6% in de-escalating therapy. In our study, patients with wall thickening (74%), mucosal enhancement (65%), mural stratification (29%) and stenosis (28%) detected by the CTE or MRE were more likely to have a change in management plans. However, the only statistically significant association found was the presence of mural stratification (p = 0.019). Escalating therapy was more commonly associated with bowel wall thickening (74%), mucosal enhancement (69%), mural stratification (29%) and stenosis (32%), whereas bowel wall thickening (74%), mucosal enhancement (56%), mural stratification (28%) and comb sign (28%) were more often related to de-escalating therapy.

Among the changes in management plan, the presence of 2 or 3 signs is the most common combination (24% and 22%, respectively). However, 5 or 6 signs are more frequently associated with changes in the therapeutic scheme. Table 8 shows the relationship between the number of radiological signs and the outcome.

Association between specific CTE or MRE findings and specific outcomes

For patients whose outcome consisted of the introduction of an immunomodulator (table 9), the most common CTE and MRE findings were: bowel wall thickening (82%), mural hyperenhancement (79%), mural stratification (38%), presence of fistulae (27%) and presence of stenosis (27%). Mural hyperehancement and

mural stratification on CTE and MRE were strongly related to this specific outcome (*p* values of 0.016 and 0.019, respectively).

The presence of ulcers, abscesses, and stenosis most commonly led to the introduction of an anti-TNFα agent (table 10). The CTE and MRE findings reported in the only case where the outcome was the increase of the dose of the immunomodulator (table 11) were mural hyperenhancement and the presence of ulcerative disease. All radiological signs of active disease showed a higher frequency for increasing the dose of anti-TNFα agent (table 12) compared to not changing the management plan, except in the presence of an abscess. In the group of patients who changed to a different immunomodulator (table 13), the CTE and MRE finding that was most frequently related with this outcome was the presence of stricturing disease. It is noteworthy that none of these associations were found to be statistically significant.

In the only case whose outcome consisted of shortening the interval between the administration of an anti-TNFα agent (table 14), only the ulcerative and structuring disease were found. However, only the association of ulcerative disease with this outcome was found to be statistically relevant (p= 0.023).

Discussion

CTE and MRE have an established role in evaluating patients with CD, by providing additional information to clinical and endoscopic assessment, which is crucial for proper patient management.[17]

Ileocolonoscopy is the gold-standard for assessment of ileocolonic CD, although the examination has certain limitations[12], such as the inability to determine disease severity in the small bowel and to evaluate extraluminal complications. CTE and MRE should represent an important step in the diagnostic, therapeutic and prognostic management of the disease in order to their ability to evaluate not only the intestinal mucosa, but also the entire bowel wall, and to detect extra luminal complications. [18,19] CTE and MRE have a high and comparable sensitivity (85.8% vs. 87.9%) and specificity (83.6% vs. 81.2%) for active small bowel inflammation and can objectively assess response to medical therapy. [11,13] Our study aimed to determine how specific CTE and MRE findings influenced gastroenterologists' therapeutic decisions for

patients with CD. Thereunto, we evaluated 349 patients with a previously established diagnosis of CD. In contrast to other studies, we simultaneously evaluated patients who had undergone a CTE (85% of the sample) and a MRE (15%).

The present study demonstrated that CTE and MRE alter the management plans in 40% of patients with established CD, which is in line with a previous report by a related study from Bruining et al[7]. His team verified that CTE changes the management plans in more than 50% of patients with established or suspected CD. In another study, Bruinning et al[20] also demonstrated that the CTE finding of penetrating disease significantly alter management plans, including the start of antibiotic therapy, surgical referral, and the use of immunosuppressive or biologic agents. Booya et al[21] described the detection of occult penetrating disease by CTE, leading to a change in management in 61% of patients with CD. On the other hand, Figueiredo et al[22] found that MRE played a decisive role in clinical decision making, leading to a change in management plans in more than half of patients. This study also confirms a previous retrospective report by Mendonza et al[23], in which MRE findings were useful for escalating medical treatment for almost 50% of patients in whom it was performed for the purpose of monitoring medical treatment.

When compared to previously studies, the patients who underwent CTE or MRE in our study were more likely to have the age at the time of diagnosis <40 years old (84%), small bowel disease (89%) and more complex disease behavior as shown by the high proportion of patients with stricturing and penetrating disease (53%). Age at the time of diagnosis <40 years old, small bowel disease and stricturing and penetrating disease (bowel damage) are some of the prognostic factors for severe disease and development of complications. [24] In a previous retrospective study by Mendonza et al[23] 70% of the cases were under 40 years old at the time of diagnosis, 65% had small bowel disease and 49% had stricturing or penetrating disease. However, in both studies, 24% of the cases had undergone previous surgery. In another study, Messaris et al[25] studied a sample of 120 patients diagnosed or suspected of CD, of which 83% were diagnosed at the age of 40, 83% had small bowel disease, and 23% were found to have stricturing or penetrating diseases. Therefore, we can assume that our sample of patients with CD was more likely to have a more complex phenotype of the disease compared with other studies. Consequently, it is not surprising that the most common outcomes in the present

study include the addition of potent anti-inflammatory medications: immunomodulators (10%), anti-TNFα agents (8%) and corticosteroids (6%).

When comparing the reason and the context of the CTE and MRE with the outcome (table 5), we found that patients who underwent CTE or MRE for CD follow-up and within the context of a consultation were more likely to have no change in their management plan (65% and 63% vs. 35% and 37%, respectively). On the contrary, for patients who underwent CTE or MRE due to acute CD complication and for those who were hospitalized, a greater proportion presented changes in the outcome (56% and 54% vs. 44% and 46%, respectively), particularly with escalating therapy (42% of 56%). These results are most likely related to the severity and acute presentation of the disease.

In the present study, 17% of the 349 CTE and MRE performed were considered normal, and, of those, 30% had a change in outcome. The remaining 83% of the patients had an abnormal CTE or MRE, of which 42% had a change in their management plan. However, unlike the study of Rajabi et al[5] we were not able to find a statistically significant association between these two variables. In their study, they found that having an abnormal MRE was strongly associated with a change in management (p=0.008).

The most frequent CTE/MRE findings were bowel wall thickening (71%) and mural hyperenhancement (60%). Bowel wall thickening (bowel wall greater than 3mm in thickness) is often asymmetric, usually more prominent along the mesenteric border. Mural hyperenhancement is the most relevant finding for active disease and corresponds to a segmental attenuation greater than the adjacent normal small bowel loops.[26,27] This CTE/MRE findings were the most commonly signs associated with change in management (74% of the patients with bowel wall thickening and 65% with mural hyperenhancement). This data is similar to a retrospective study by Rajabi et al[5], which demonstrated that patients who had a change in management were more likely to have findings of circumferential wall thickening on MRE, as well as reactive lymph nodes. Another abnormality associated with active disease is comb sign (engorgement of *vasa recta*), but it has limited sensitivity and specificity for determining the presence of active inflammation.[28] In the present study, comb sign was present in 22% of the

patients and was more commonly associated with no change in management than with a change in outcome (55% and 46%, respectively, with $p>0.05$).

In addition to the signs of active disease, grading the severity of lesions is of vital importance in clinical practice since it has therapeutic and prognostic implications. The CTE and MRE findings associated to severe disease are the presence of edema, ulcerations, structuring disease and penetrating disease.[28] Mural stratification (figures 1 and 2) was present in 22% of the patients in the present study. This radiologic signal refers to a laminated appearance of thickened wall, due to mural edema. [26] It has been suggested that mural hyperenhancement, without stratification, may be more common in the early stages of CD, whereas mural stratification may indicate more advanced disease. [3] Furthermore, mural edema is predominantly identified in segments with severe inflammatory lesions. [28] In our study, we have found that the only CTE/MRE finding that correlates significantly with change in management was mural stratification ($p<0.05$), which may be related to more advanced and severe disease in those patients. Furthermore, mural hyperenhancement and mural stratification were significantly associated with the introduction of immunomodulator ($p=0.016$ and $p=0.019$, respectively), corresponding to 79% and 38% of CTE/MRE findings associated with this outcome. Ulcerations are more commonly found on the mesenteric border of the bowel and their appearance may vary from subtle lesions (fissuring ulcerations) to deep lesions in a thickened hyperenhanced wall. [28] Presence of ulcerating disease was shown to lead more commonly to an escalation in therapy (50%) than to no change in the management plan (38%) or de-escalating therapy (13%).

Fibrostenosing and penetrating disease are the main complications of CD. Abscess, fistulae and stenosis are clearly signs of bowel damage, and the proportion of patients developing these complications increases over the years after a diagnosis of CD. [19] Cross-sectional imaging, specifically CTE and MRE, are essential in the evaluation of these complications, since, unlike endoscopic methods, they are able to delineate fistulous pathways, detect abscesses, and identify, locate and evaluate the extent of stricturing processes.[28] In our study, the presence of fistulae, abcesses and stenosis were more commonly associated with the introduction of an immunomodulator and with the introduction of an anti-TNFα agent when compared to other outcomes. However, only stenosis were marginally associated with a change in management ($p=0.067$), but none of these findings were found to be strongly correlated with any

outcome (p>0.05). In contrast, Rajabi et al[5] found that the presence of an abcess or phlegmon on MRE was significantly associated (p= 0.03) with a change in management, but they were not able to find a significant association between the presence of fistulae and a change in management.

The increased accessibility of cross-sectional imaging methods in recent years has led to an increase in the number of CT scans prescribed. Factors like young age at the time of diagnosis, the recurrent nature of the disease and the introduction of biological therapies, are related to the increased use of CTE and, consequently, to a higher cumulative radiation exposure. Thus, since MRE is a radiation-free method, it is the preferred cross-sectional imaging technique for monitoring patients with CD.[29] Scoring of disease activity is important for objective assessment, and several indices have been proposed. Rimola et al[29] proposed and validated the most widely used MRE score - MaRIA score - that includes wall thickening, mucosal hyperenhancement and presence of edema and ulcers. This index has been successfully validated using a cohort of 49 patients and ileocolonoscopy as the reference standard.[14] It was demonstrated that the MaRIA score has a high accuracy for detection of active disease, severe disease, while also providing an objective, quantitative and reproducible measure of disease activity.[14] Notwithstanding, this score does not appear to guide the management of CD patients and does not take into account important parameters concerning CD severity, such as the presence of stricturing disease or penetrating disease. Therefore, the development of severity scores that take these signs into account is relevant, providing important additional information about the real activity of the disease and allowing clinicians to make more informed decisions about the best therapeutic option for each case. In our study, several CTE and MRE findings were shown to be strongly related to specific outcomes: mural hyperenhancement and mural stratification with the introduction of an immunomodulator; and ulcerative disease with shortening of the interval between the administration of an anti-TNFα agent. These results lead us to believe that specific CTE and MRE findings, and perhaps new disease scoring systems, may help to stratify treatment options. However, further studies are required to validate this.

Our study highlights the importance of CTE and MRE features on the outcome of patients with CD, providing additional data about parameters that are most likely to influence clinicians' management plans of these patients. However, several limitations

of this study are evident. Given its retrospective nature, the existence of evaluation and detection biases is a possibility. Many patients had incomplete clinical data, which may have also influenced the results. Moreover, the elaboration of CTE and MRE reports by different radiologists and their evaluation and interpretation by non-radiologists may also be a factor of subjectivity and bias in the study. To prove the value of CTE and MRE in clinical assessment of CD, prospective studies are needed to determine whether the information obtained from CTE/MRE actually changes clinical decision making and clinical outcomes, and how can these imaging techniques contribute as a guide to the best therapeutic decisions.

In conclusion, the goal of our study was to retrospectively assess the impact of CTE and MRE on the therapeutic decision making for patients with CD. We found that CTE and MRE in CD patients presented important information, regarding disease activity and behavior, which played a decisive role in clinical decision making, leading to a therapeutic change in 40% of patients. Furthermore, mural stratification, a sign of CD's severity, showed to be strongly related with the outcome. These data provide additional support favoring the routine use of these imaging techniques in the monitoring and therapeutic management for patients with CD.

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Tables

Table 1. Baseline characteristics of patients with Crohn's Disease who were included in the study (CTE – Computed Tomography Enterography; MRE – Magnetic Resonance Enterography)

	n (%)
Demographics	
Female	161 (46)
Male	188 (54)
Median age (range)	34 (11-76)
Age < 18 years old	33(10)
Age at diagnosis	
A1	69 (20)
A2	218 (64)
A3	54 (16)
Behaviour	
B1	162 (48)
B2	77 (23)
B3	102 (30)
P	74 (22)
Location	
L1	158 (45)
L2	38 (11)
L3	152 (44)
L4	63 (18)
CTE's and MRE's Reason	
Follow-up	271 (78)
Acute complication	78 (22)
CTE's and MRE's context	
Appointment	291 (83)
Internment	58 (17)
History of Hospitalization	235 (67)
History of Surgery	83 (24)

Table 2. Computed Tomography Enterography and Magnetic Resonance Enterography findings

	n (%)
Bowel wall thickening	249 (71)
Mucosal enhancement	210 (60)
Mural stratification	78 (22)
Comb sign	77 (22)
Ulcer	8 (2)
Fistulae	66 (19)
Abscess	11 (3)
Stenosis	83 (24)
None	60 (17)

Table 3. Categorization of the outcomes in study

No change in management	Escalating therapy	De-escalating therapy
	1. Introduction of immunomodulator	1. Suspension of immunomodulator
	2. Introduction of anti-TNF agent	2. Suspension of anti-TNF agent
	3. Dose increase of immunomodulator	3. Dose decrease of immunomodulator
	4. Dose increase of anti-TNF agent	4. Dose decrease of anti-TNF agent
	5. Shortening the interval between administrations of anti-TNF agent	5. Extending the interval between administrations of anti-TNF agent
	6. Change to a different immunomodulator	6. Suspension of corticosteroids
	7. Change to a different anti-TNF agent	7. Decreased corticosteroid dose
	8. Introduction of corticosteroid	8. Suspension of aminosalicylates
	9. Dose increase of corticosteroid	9. Suspension of polymeric diet
	10. Introduction of aminosalicylates	
	11. Introduction of polymeric diet	
	12. Surgery	

Table 4. Frequency of the outcomes

Outcome	n (%)
No change in management	210 (60)
Escalating therapy	
Introduction of immunomodulator	34 (10)
Introduction of anti-TNFα agent	28 (8)
Dose increase of immunomodulator	1 (0)
Dose increase of anti-TNFα agent	13 (4)
Shortening the interval between administrations of anti-TNFα agent	1 (0)
Change to a different immunomodulator	3 (1)
Change to a different anti-TNFα agent	0 (0)
Introduction of corticosteroid	20 (6)
Dose increase of corticosteroid	1 (0)
Introduction of aminosalicylates	7 (2)
Introduction of polymeric diet	0 (0)
Surgery	0 (0)
De-escalating therapy	
Suspension of immunomodulator	11 (3)
Suspension of anti-TNFα agent	5 (1)
Dose decrease of immunomodulator	4 (1)
Dose decrease of anti-TNFα agent	0 (0)
Extending the interval between administrations of anti-TNFα agent	0 (0)
Corticosteroids suspension	1 (0)
Decreased corticosteroid dose	18 (5)
Suspension of aminosalicylates	3 (1)
Suspension of polymeric diet	9 (3)
Suspension of immunomodulator	4 (1)

Table 5. Reason and context in which the Computed Tomography Enterography and Magnetic Resonance Enterography were carried out and their repercussion on the clinical management for the CD patients in study (0 – No change in management plan; 1 – Escalating therapy; 2 – De-escalating therapy; R/C– Reason/Context; Out – Outcome)

	Outcome									***p***
	0			**1**			**2**			
	n=210			n=96			n=43			
	n	**%R/C**	**%Out**	**n**	**% R/C**	**%Out**	**n**	**% R/C**	**%Out**	
Follow-up	175	65	83	63	23	66	32	12	74	**0.002**
Acute complication	35	45	17	32	42	33	11	14	26	**0.004**
Appointment	184	63	88	73	25	76	35	12	81	**0.036**
Internement	26	46	12	23	40	24	8	14	18	**0.036**

Table 6. The impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on patients' outcome (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Outcome						***p***
	0			**1**			
	n=210			n=139			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	42	70	20	18	30	13	0,087
Bowel wall thickening	146	59	70	103	41	74	0,355
Mucosal enhancement	120	57	57	90	43	65	0,155
Mural estratification	38	49	18	40	51	29	**0,019**
Comb sign	42	55	20	35	46	25	0,253
Ulcer	3	38	1	5	63	4	0,274
Fistulae	35	53	17	31	47	22	0,188
Abscess	6	55	3	5	46	4	0,759
Stenosis	44	53	21	39	47	28	0,127

Table 7. The impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on patients outcome (0 – No change in management plan; 1 – Escalating therapy; 2 – De-escalating therapy; RS – Radiological Signs; Out – Outcome)

	Outcome									***p***
	0			**1**			**2**			
	n=210			n=96			n=43			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	42	70	20	12	20	13	6	10	14	0,227
Bowel wall thickening	146	59	70	71	29	74	32	13	74	0,650
Mucosal enhancement	120	57	57	66	31	69	24	11	56	0,129
Mural estratification	38	49	18	28	36	29	12	15	28	**0,063**
Comb sign	42	55	20	23	30	24	12	16	28	0,455
Ulcer	3	38	1	4	50	4	1	13	2	0,185
Fistulae	35	53	17	20	30	21	11	17	26	0,338
Abscess	6	55	3	3	27	3	2	18	5	0,699
Stenosis	44	53	21	31	37	32	8	10	19	**0,067**

Table 8. Number of Computed Tomography Enterography and Magnetic Resonance Enterography findings and their repercussion on the outcome of CD patients (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Outcome						***p***
	0			**1**			
	n=210			n=139			
CTE/MRE findings	**n**	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
0	42	71	20	17	29	12	
1	29	59	14	20	41	14	
2	61	65	29	33	35	24	
3	44	59	21	31	41	22	0,115
4	22	52	11	20	48	14	
5	10	42	5	14	58	10	
6	2	33	1	4	67	3	

Table 9. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Introduction of immunomodulator (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Introduction of immunomodulator						**p**
	0			**1**			
	n=315			n=34			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	59	98	19	1	2	3	**0.020**
Bowel wall thickening	221	89	70	28	11	82	0.135
Mucosal enhancement	183	87	58	27	13	79	**0.016**
Mural estratification	65	83	21	13	17	38	**0.019**
Comb sign	71	92	23	6	8	18	0.513
Ulcer	7	88	2	1	13	3	0.563
Fistulae	57	86	18	9	14	27	0.236
Abscess	9	82	3	2	18	6	0.291
Stenosis	74	89	24	9	11	27	0.698

Table 10. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Introduction of anti-TNFα agent (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Introduction of anti-TNFα agent						**p**
	0			**1**			
	n=321			n=28			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	52	87	16	8	13	29	0.115
Bowel wall thickening	233	94	72	16	6	57	0.083
Mucosal enhancement	194	92	60	16	8	57	0.733
Mural estratification	74	95	23	4	5	14	0.286
Comb sign	74	96	23	3	4	11	0.131
Ulcer	7	88	2	1	13	4	0.491
Fistulae	61	92	19	5	8	18	0.882
Abscess	10	91	3	1	9	4	0.605
Stenosis	76	92	24	7	8	25	0.875

Table 11. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Dose increase of immunomodulator (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Dose increase of immunomodulator						**p**
	0			**1**			
	n=348			n=1			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	60	100	17	0	0	0	1.000
Bowel wall thickening	249	100	72	0	0	0	0.287
Mucosal enhancement	209	100	60	1	0	100	1.000
Mural estratification	78	100	22	0	0	0	1.000
Comb sign	76	99	22	0	0	0	0.221
Ulcer	8	100	2	1	2	100	1.000
Fistulae	65	99	19	0	0	0	0.189
Abscess	11	100	3	0	0	0	1.000
Stenosis	82	99	24	1	1	100	0.238

Table 12. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Shortening the interval between administrations of anti-TNFα agent (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Shortening the interval between administrations of anti-TNFα agent						**p**
	0			**1**			
	n=348			n=1			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	60	100	17	0	0	0	1.000
Bowel wall thickening	249	100	72	0	0	0	0.287
Mucosal enhancement	210	100	60	0	0	0	0.398
Mural estratification	78	100	22	0	0	0	1.000
Comb sign	77	100	22	0	0	0	1.000
Ulcer	7	84	2	1	13	100	**0.023**
Fistulae	66	100	19	0	0	0	1.000
Abscess	11	100	3	0	0	0	1.000
Stenosis	82	99	24	1	1	100	0.238

Table 13. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Dose increase of anti-TNFα agent (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Dose increase of anti-TNF agent						**p**
	0			**1**			
	n=336			n=13			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	59	98	18	1	2	8	0.706
Bowel wall thickening	239	96	71	10	4	77	0.765
Mucosal enhancement	200	95	60	10	5	77	0.209
Mural estratification	75	96	22	3	4	23	1.000
Comb sign	72	94	21	5	7	39	0.171
Ulcer	7	88	2	1	13	8	0.264
Fistulae	62	94	19	4	6	31	0.279
Abscess	11	100	3	0	0	0	1.000
Stenosis	79	95	24	4	5	31	0.517

Table 14. Impact of specific Computed Tomography Enterography and Magnetic Resonance Enterography findings on specific outcomes – Change to a different immunomodulator (0 – No change in management plan; 1 – Change in management plan; RS – Radiological Signs; Out - Outcome)

	Change to a different immunomodulator						**p**
	0			**1**			
	n=346			n=3			
	n	**%RS**	**%Out**	**n**	**%RS**	**%Out**	
None	60	100	17	0	0	0	1.000
Bowel wall thickening	247	99	71	2	1	67	1.000
Mucosal enhancement	209	100	60	1	0	33	0.566
Mural estratification	77	99	22	1	1	33	0.533
Comb sign	77	100	22	0	0	0	1.000
Ulcer	8	100	2	0	0	0	1.000
Fistulae	66	100	19	0	0	0	1.000
Abscess	11	100	3	0	0	0	1.000
Stenosis	82	99	24	2	1	33	0.558

Figure Legends

Figure 1. Stratified appearance in Crohn's Disease. Axial and coronal contrast-enhanced Computed Tomography Enterography scan of the abdomen shows concentric wall thickening of small bowel loop with a stratified appearance indicating active disease. Also note a fistula connecting the bowel loops, a common finding in penetrating subtype of Crohn's Disease.

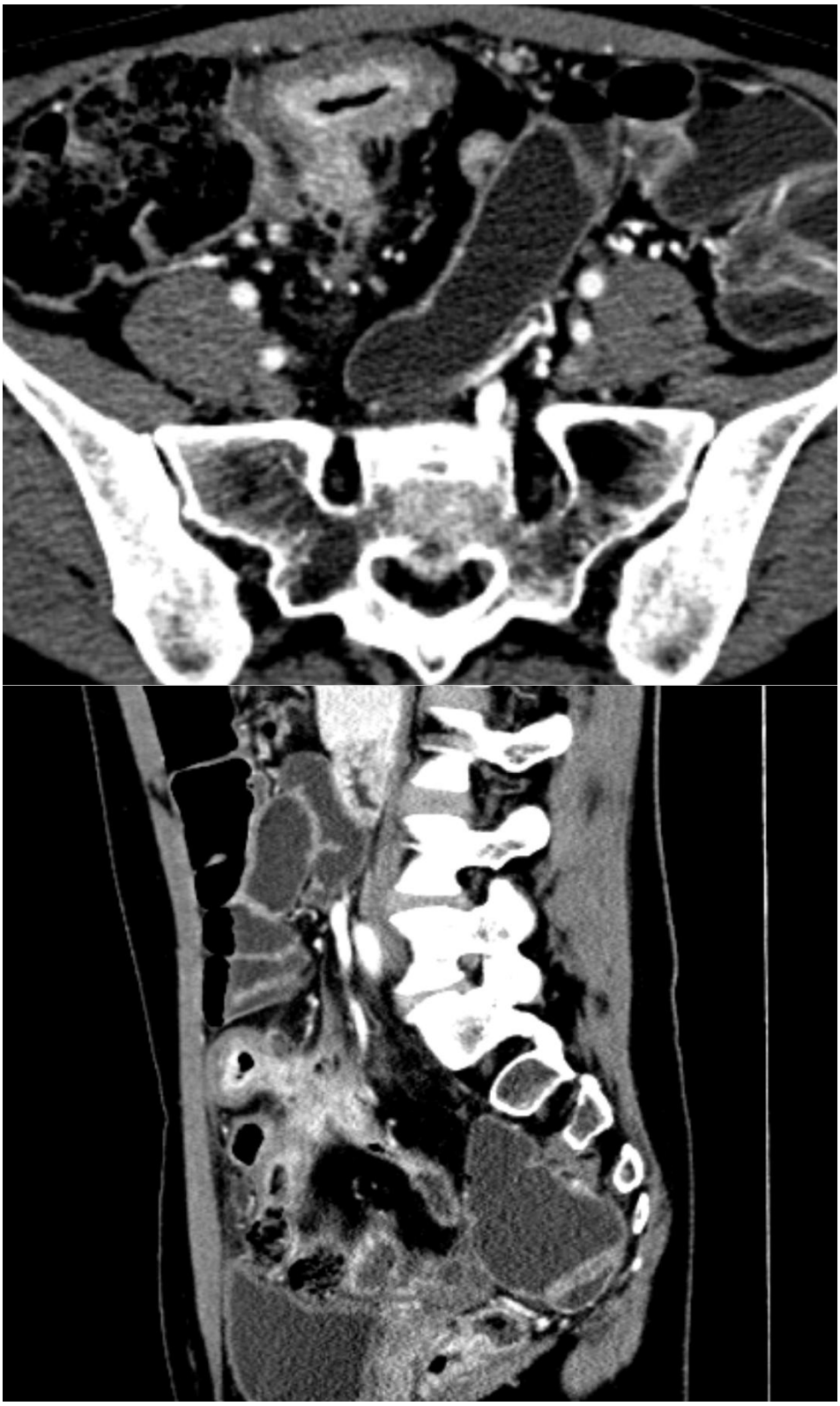
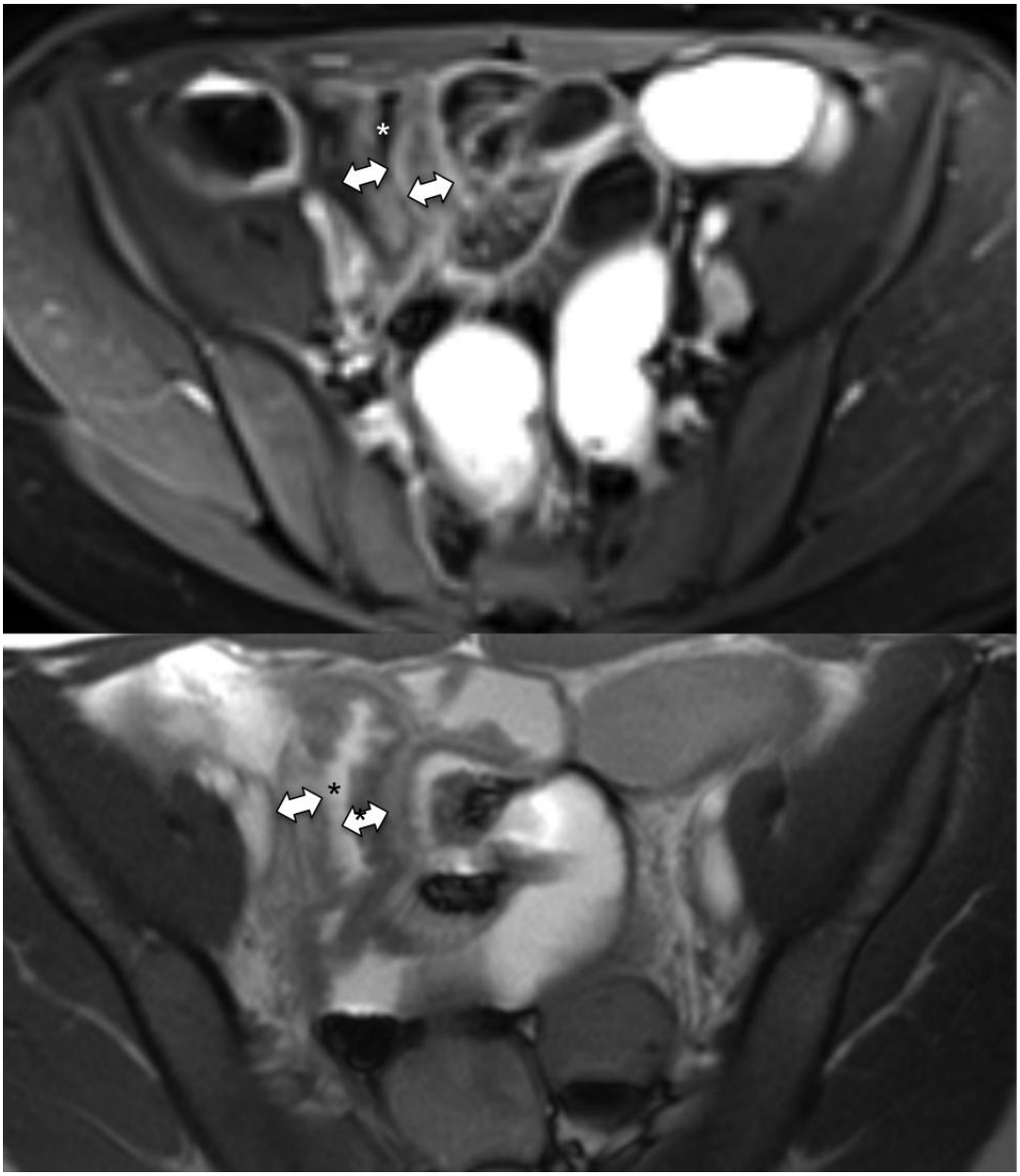


Figure 2. Axial contrast enhanced and T2 haste images of Magnetic Resonance Enterography show bowel wall thickening (double arrows), luminal fluid (*) and bowel wall stratification with mucosal and serosal avidly enhancing when compared to submucosa, in a patient with Crohn´s Disease.



Anexos

Inflammatory Bowel Diseases

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Sample references are given below:

Journal Article

1. Gudlaugsdottir S, van Dekken H, Stijnen T, et al. Prolonged use of proton pump inhibitors, CagA status, and the outcome of Helicobacter pylori gastritis. *J Clin Gastroenterol*. 2002;34:536-540.

Book Chapter

2. Tobin RW, Kimmey MB. Painful diseases of the gastrointestinal tract. In: Loeser JD, ed. *Bonica's Management of Pain*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:1269-1292.

Entire Book

3. Rohen JW, Yokochi C, Lütjen-Drecoll E. *Color Atlas of Anatomy: A Photographic Study of the Human Body*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.

Software

4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994.

Online Journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. ObstetGynecol [serial online]. January 1988;71:22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 2014. Updated March 29, 2014.

World Wide Web

7. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 2015. Available at: http://www.ama-assn.org/special/hiv/ethics,. Accessed July 26, 2015.

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